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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,784	06/06/2005	Michal Amit	29606	5082

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,784	AMIT ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *153-229* is/are pending in the application.

4a) Of the above claim(s) *218-220* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *153-217 and 221-229* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election of group I, claims 153-217 and 221-229, in the reply filed on November 7, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 218-220 have been withdrawn from consideration as to a non-elected invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 164, 165, 168, 169, 182, 183, 194, 195, 198, 199, 210, 211, 214, 215, 226 and 228 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 164, 165, 168, 169, 182, 183, 194, 195, 198, 1999, 210, 211, 214, 215, 226 and 228 are drawn to methods of culturing ES cells or hES cells, and ES or hES cell cultures where the culture media contains TGFβ1 or LIF. However, the art at the time of filing taught that neither of these growth factors can maintain ES cells in a proliferative, pluripotent and undifferentiated state. Bodnar taught the primate ES cells in the cultured in media containing TGFβ1 began to differentiate as indicated by a greater than 20% decrease in alkaline phosphatase activity (Bodnar, page 25, lines 2-5 and Table 3, line 4). Schuldiner taught TGFβ1 inhibits endoderm and ectodermal cell differentiation but permits mesodermal cell differentiation (Schuldiner, page 11311, col. 1, parag. 1, lines 4-6). Likewise, LIF has been shown not to maintain hES cells in an undifferentiated state (Thomson, page 1146,

col. 1, parag. 2, lines 13-18). Further it is noted the specification discloses hES cells have begun to differentiate at six days in culture when the media contains TGFβ1, βFGF, LIF and TGFβ1, or LIF and βFGF (specification, page 39, lines 20-23). Thus, TGFβ1 or LIF are not sufficient to maintain primate ES cells in a proliferative, pluripotent and undifferentiated state as claimed and disclosed in the specification. Therefore at the time of filing the skilled artisan would have needed to engage in an undue amount of experimentation without a predictable degree of success to implement the invention of the claims.

Claim 229 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of maintaining hES cells in an undifferentiated, pluripotent and proliferative state under culture conditions devoid of feeder cells, the method comprising culturing hES cells on an *extracellular* matrix, in the present of media comprising 15% serum replacement, 0.12 ng/ml TGFβ1, 1000 u/ml LIF and 4 ng/ml βFGF, wherein said cells are maintained for at least 56 passages with a doubling time of at least 25 hours, does not reasonably provide enablement for a method of maintaining hES cells in an undifferentiated, pluripotent and proliferative state under culture conditions devoid of feeder cells, the method comprising culturing hES cells on a matrix, in the present of media comprising 15% serum replacement, 0.12 ng/ml TGFβ1, 1000 u/ml LIF and 4 ng/ml βFGF, wherein said cells are maintained for at least 56 passages with a doubling time of at least 25 hours. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches several extracellular matrices (MEF, Matrigel™, foreskin fibroblast and bovine/human fibronectin) support the growth and pluripotency of hES cells (specification, page 40, lines 9-23). However, a matrix such as a culture dish is known to cause the formation of EB's, which are not pluripotent cells, but are cells of mesodermal,

ectodermal and endodermal lineages (specification, page 33, lines 5-10). Thus, the generic term "matrix" is not enabled, but rather "extracellular matrix is. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 153, 155, 156, 159-163, 166, 170-177, 180, 181, 184, 188, 189, 200-203, 209, 212, 216, 217, 221-223, 225 and 227 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by WO 99/20741 published April 29, 2000 (Bodnar).

Bodnar teaches methods of establishing a xeno-free, feeder cell-free hES cells line, a method propagating a species embryonic stem cell line in a undifferentiated, pluripotent and proliferative state and methods of maintaining human embryonic stem cells by the culture of PSC43 cells in a media comprising 20% FCS, rhesus monkey ES cells, on an MEF matrix or a fibronectin matrix in the presence of βFGF (page 2, lines 24-28; page 3, lines 10-13; page 12, lines 8-10; page 20, lines 14-17; page 24, line 23 to page 25, line 2; page 25, Table 2, lines 8 and 11; page 26, line 25 to page 27, line 3; page 27, Table 4, esp. line 5). Bodnar teaches culturing PSC43 cells in media supplemented with 1.25 ng/ml or about 5 ng/ml βFGF or supplemented with 1.0 ng/ml or about 1.2 ng/ml LIF (page 9, lines 23-24; page 15, lines 8-11;

page 25, Table 2, line 8). Further Bodnar teaches the culture of PSC43 cells on a matrix in species-conditioned media (page 19, lines 4-16). Bodnar teaches the method results in the proliferation of undifferentiated, pluripotent PSC43 cells. The method of Bodnar results in a cell culture comprising undifferentiated, pluripotent and proliferative hES cells in a culture medium where the culture is substantially free of xeno and feeder cell contaminants (page 11, lines 10-11; page 6, lines 11-13; page 19, lines 4-16). Further, Bodnar teaches the methods taught can be used to maintain human ES cells (page 6, lines 11-13; page 11, lines 10-11).

The specification offers no definition of the term "xeno free," thus, the lack of feeder is seen a rendering the cell culture of Bodnar "xeno free". Bodnar's culture is free of cell contaminants and thus is "xeno free." It is noted certain claims, such as claim 170, uses terminology "capable of." This does not require a positive attribute to the product or method claimed as the only requirement is that the method or the product under certain conditions may have the limitation claimed. Applicant should consider rewriting the claim to positively state the capable of attribute. The fibronectin used in Bodnar is inherently derived from a species. As the method steps claimed and those of Bodnar are the same, it is an inherent properly of Bodnar that the cell would comprise at least 85% undifferentiated species ES cells and have a doubling time of at least 25 hours.

Therefore Bodnar anticipates the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 153, 154, 167, 170, 176, 178-181, 185-187, 190-193, 196, 197, 203, 206-209 and 213 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/20741

published April 29, 2000 (Bodnar) in view of Amit et al. (2000) Devel. Biol., Vol. 227, pp. 271-278 (Ref. 5, IDS 10/24/06).

Bodnar teaches methods of establishing a xeno-free, feeder cell-free hES cell line, a method propagating a species embryonic stem cell line in a undifferentiated, pluripotent and proliferative state by the culture of PSC43 cells in a media comprising 20% FCS, rhesus monkey ES cells, on an MEF matrix or a fibronectin matrix in the present of LIF or βFGF (page 2, lines 24-28; page 3, lines 10-13; page 12, lines 8-10; page 20, lines 14-17; page 24, line 23 to page 25, line 2; page 25, Table 2, lines 8 and 11; page 26, line 25 to page 27, line 3; page 27, Table 4, esp. line 5). Further Bodnar teaches the culture of PSC43 cells on a matrix in species-conditioned media (page 19, lines 4-16). Bodnar teaches the method results in the proliferation of undifferentiated, pluripotent PSC43 cells. The method of Bodnar results in a cell culture comprising undifferentiated, pluripotent and proliferative hES cells in a culture medium where the culture is substantially free of xeno and feeder cell contaminants (page 11, lines 10-11; page 6, lines 11-13; page 19, lines 4-16). Further, Bodnar teaches the methods taught can be used to maintain human ES cells (page 6, lines 11-13; page 11, lines 10-11). Bodnar teaches culturing PSC43 cells in media supplemented with 1.25 ng/ml or about 5 ng/ml βFGF or supplemented with 1.0 ng/ml or about 1.2 ng/ml LIF (page 9, lines 23-24; page 15, lines 8-11; page 25, Table 2, line 8).

Amit teaches culturing hES cells on MEF feeder cells in media containing 20% serum replacement, KnockOut SR (page 272, col. 1, parag. 2, lines 4-11) and 4 ng/ml bFGF (page 273, Figure 1 and col. 1, lines 7-12). Amit also teaches cloning H9 cells (page 273, parag. 1, lines 1-7). Amit states serum free medium enhanced cloning efficiency several fold over serum containing media (page 272, col. 2, parag. 5, line 1 to page 273, line 1).

Amit offers motivation in stating the addition of bFGF to the culture media improved cloning efficiencies, and was required for continued undifferentiated proliferation (page 273, col. 1, lines 7-10). Amit offers additional motivation in stating cloning H9 cells would eliminate the

possibility that a colony originated from clumps of cells remaining after dissociation (page 273, col. 1, parag. 1, lines 1-6).

Thus at the time of the instant invention it would have been obvious to the ordinary artisan to establish a xeno-free, feeder cell-free ES or hES cell line, propagate a species ES cell line in an undifferentiated, pluripotent and proliferative state and a cell culture comprising undifferentiated, pluripotent, proliferative hES cells by modifying the primate ES cell line culture as taught by Bodnar and also taught by Bodnar to be useful for culturing human ES cell lines, with the modifications of serum containing a serum placement, culturing in the presence of 4 ng/ml bFGF and cloning the ES cells, each taught by Amit and for the motivation provided by Amit. A reading of Bodnar and Amit indicates the art was actively seeking optimum culture conditions for hES cells.

Claims 153, 156-158, 203-205, 221, 223 and 224 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/20741 published April 29, 2000 (Bodnar) in view of the Sigma Catalog, 1992, page 1389, cat. nos. F 2518 and F2006..

Bodnar teaches methods of establishing a xeno-free, feeder cell-free hES cell line, a method propagating a species embryonic stem cell line in a undifferentiated, pluripotent and proliferative state by the culture of PSC43 cells in a media comprising 20% FCS, rhesus monkey ES cells, on an MEF matrix or a fibronectin matrix in the present of LIF or βFGF (page 2, lines 24-28; page 3, lines 10-13; page 12, lines 8-10; page 20, lines 14-17; page 24, line 23 to page 25, line 2; page 25, Table 2, lines 8 and 11; page 26, line 25 to page 27, line 3; page 27, Table 4, esp. line 5). Further Bodnar teaches the culture of PSC43 cells on a matrix in species-conditioned media (page 19, lines 4-16). Bodnar teaches the method results in the proliferation of undifferentiated, pluripotent PSC43 cells. The method of Bodnar results in a cell culture comprising undifferentiated, pluripotent and proliferative hES cells in a culture medium where the culture is substantially free of xeno and feeder cell contaminants (page 11, lines 10-11; page 6, lines 11-13; page 19, lines 4-16). Further, Bodnar teaches the methods taught can be used to

maintain human ES cells (page 6, lines 11-13; page 11, lines 10-11). Bodnar teaches culturing PSC43 cells in media supplemented with 1.25 ng/ml or about 5 ng/ml βFGF or supplemented with 1.0 ng/ml or about 1.2 ng/ml LIF (page 9, lines 23-24; page 15, lines 8-11; page 25, Table 2, line 8).

The Sigma/Aldrich teaches human fibronectin isolated from human foreskin and human plasma, and their use at cell attachment matrices in cell culture (page 1389, parag. 1 and col. 2, F 2518 and F 2006).

Thus at the time of filing, it would have been obvious to the ordinary artisan to use human fibronectin in view of Bodnar teaching increase hES cell proliferation when grown on fibronectin and the Sigma catalog teaching the availability of human plasma and human foreskin fibronectin, and the use of fibronectin as a cell culture matrix. The substitution of one fibronectin for another fibronectin to enhance growth, viability, pluripotency of hES cells is obvious absence results to the contrary.

The combination of prior art cited above in both rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are

predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention." Thus, the teachings of Bodnar and Amit, and Bodnar and the Sigma/Aldrich Catalog together provide the teachings and motivations to modify the methods and cells of Bodnar by the methods of Amit or modify the methods of Bodnar with the human fibronectin taught by Sigma/Aldrich with a clear, reasonable expectation. The cited prior art meets the criteria set forth in both Graham and KSR.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 6:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

January 22, 2008